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Review

Innate immunity and tolerance toward mitochondria

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ABSTRACT

Mitochondria are intracellular organelles that originate from a bacterial symbiont, and they retain multiple features of this bacterial ancestry. The immune system evolved to detect the presence of invading pathogens, including bacteria, to eliminate them by a diversity of antimicrobial mechanisms and to mount long-term protective immunity. Due to their bacterial ancestry, mitochondria are sensed by the innate immune system, and trigger inflammatory responses comparable to those induced by pathogenic bacteria. In both cases, innate sensing mechanisms involve Toll-Like Receptors, Formyl Peptide Receptors, inflammasomes or the cGAS/STING pathway. Stressed mitochondria release mitochondrial molecules, such as cardiolipin and mitochondrial DNA, which are sensed as cellular damage potentially caused by infections. Recent research has identified several conditions in which mitochondrial stress-induced immunity is essential to effective antimicrobial defenses. But, in pathological conditions, the abnormal activation of the innate immune system by damaged mitochondria results in auto-inflammatory or autoimmune diseases. To prevent undesirable mitochondria-targeted responses, immune tolerance toward mitochondria must be established, involving regulation of mitophagy and mitochondrial permeability, as well as activation of specific nucleases and pro-apoptotic caspases. Overall, recent findings identify mitochondria as central in the induction of innate immunity, and provide new insights as to how immune responses to these multi-functional organelles might be exploited therapeutically in various disease states.

1. The bacterial origin of mitochondria

Mitochondria's origin traces back to an endosymbiotic event that happened about 1.5 billion years ago, when a protoeukaryotic cell engulfed an α-protobacterium and retained it as an organelle (Archibald, 2015; Zimorski et al., 2014). The newly acquired intracellular symbiont then evolved and specialized in aerobic respiration, by means of the electron transport chain and oxidative phosphorylation. This bioenergetics pathway extracts energy from glucose with high efficiency, enabling the production of 36 molecules of ATP per glucose molecule, compared to only two ATP molecules generated by glycolysis. The highly efficient mitochondrial energy production has fueled the extraordinary evolution of eukaryotic cells, from their initial unicellular state to the complexity of modern multicellular organisms. Present-day mitochondria retain at least four distinctive features of their bacterial ancestry. First, mitochondria replicate autonomously in the cytosol, independently of cell division (Archibald, 2015). Second, the mitochondrial double membrane is composed of specific phospholipids, such as cardiolipin, uniquely found in mitochondrial inner membranes and in prokaryotes, but absent from all other eukaryotic membranes (Osman et al., 2011). Third, although the vast majority of mitochondrial proteins is encoded in the nucleus, mitochondria retain their own circular DNA genome with hypomethylated CpG motifs, lacking histones and containing intronless, polycistronic genes that encode 13 mitochondrial proteins, 22 transfer RNAs and two ribosomal RNAs in vertebrates (Aanen et al., 2014; Shadel and Clayton, 1997). Fourth, like in bacteria, mitochondrial protein translation starts with a formylated methionine, an N-terminal modification never found on proteins encoded in the nuclear genome (Dahlgren et al., 2016). Therefore, modern mitochondria can be viewed as vestigial bacteria living in the cytosol of eukaryotic cells (Fig. 1A), and this ancestry has important implications for the immune system. In this review, I detail how the innate immune system detects the presence of bacteria, and how the same immune detection mechanisms are triggered by mitochondria. I then describe the tolerance mechanisms needed to prevent constitutive immunity against mitochondria. Finally, I discuss the roles of mitochondria-triggered immune responses in physiological conditions, as well as the pathological consequences of dysregulations in such responses.

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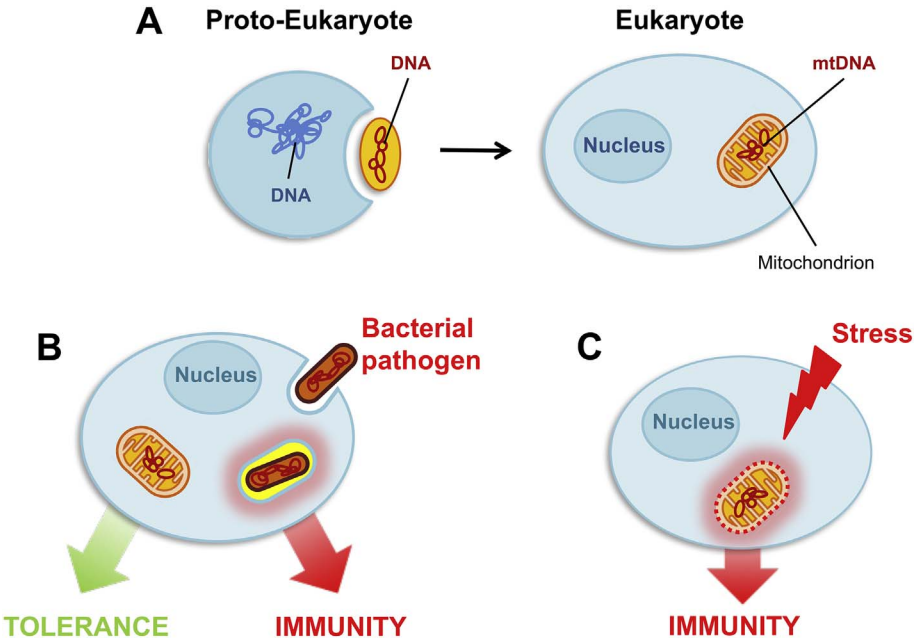

Fig. 1. Mitochondria are intracellular organelles derived from the endosymbiosis of an α-protobacterium by a proto-eukaryotic cell (A). Tolerance mechanisms are needed to prevent the recognition of mitochondria as non-self (B) and avoid anti-mitochondrial innate immunity (C).

2. The innate immune system detects bacterial infections to induce inflammation and protective immunity

Innate immunity is the first line of immune defense against invading pathogens (Medzhitov, 2007, 2010). In contrast to adaptive immunity mediated by T and B lymphocytes, innate immune responses are mounted almost instantaneously after infection, they target a limited set of molecules and generally do not result in memory development. Innate immunity functions based on the recognition by germline-encoded receptors of Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs). PAMPs are essential microbial molecules never generated by the host cell, such as bacterial cell wall or flagellum components, which constitute a characteristic microorganism molecular signature. Uniquely microbial nucleic acids represent a second important class of PAMPs. Of course, DNA and RNA are also produced by eukaryotic host cells and are not unique to pathogens. But pathogen-derived nucleic acids differ, and are therefore distinguished by innate immune receptors, owing to their specific base composition, chemical modifications, secondary structures and/or their localization in distinct cellular or extra-cellular compartments. In contrast to PAMPs that are uniquely produced by a pathogen, DAMPs (also known as alarmins) are host endogenous molecules that normally reside in a specific cellular compartment and are exposed or released after stress-induced modifications, cellular injury or death. By sensing DAMPs, the immune system is able to detect that cells are undergoing damage potentially caused by an infection, and thereby trigger anti-microbial defenses.

Innate immune sensing is performed by two categories of cells (sentinels, and all other cell types), each relying on distinct types of innate immune receptors (Iwasaki and Medzhitov, 2015). Sentinels of the immune systems, such as macrophages, neutrophils and dendritic cells, patrol the organism and survey for pathogens in the extracellular environment using receptors localized at the plasma membrane or in endosomal compartments. In contrast, most other immune and non-immune cells are equipped with cytosolic receptors for cell-autonomous detection of infection. The signaling pathways downstream of innate immune sensors activate multiple effector mechanisms that contribute to fending off infections. Antimicrobial peptides, phagocytosis, autophagy and the suicide of infected cells all participate in the direct elimination of invading pathogens. A variety of soluble effectors, including cytokines and chemokines, recruit and activate immune cells at the infection site, amplifying their antimicrobial activity. Specific immune cells migrate to draining lymph nodes, where they present pathogen-derived antigens and stimulate an adaptive immune response by T and B lymphocytes, to confer long term antigen-specific protection against the pathogen.

3. Innate immune sensors respond to both bacteria and mitochondria

Several classes of innate immune sensors are used to detect diverse types of PAMPs or DAMPs. This section focuses on the main sensors known to be involved in the detection of bacterial infections and that also respond to mitochondrial ligands: Toll-Like Receptors (TLRs), Formyl Peptide Receptors (FPRs), inflammasomes and molecules of the cGMP-AMP Synthase (cGAS)/Stimulator of IFN Genes (STING) pathway (Fig. 2).

TLRs are transmembrane proteins localized at the cell surface or in endosomal compartments, specialized in the detection of molecular patterns unique to pathogens (Akira and Takeda, 2004). TLRs involved in the detection of bacteria include TLR4 that recognizes lipopolysaccharide (LPS, a component of gram-negative bacteria membranes), TLR2 that senses different bacterial cell wall components (such as lipopeptides produced by gram-positive bacteria), TLR5 that binds flagellin (a principal component of bacterial flagella) and TLR9 that responds to unmethylated CpG DNA motifs characteristic of bacterial genomes. TLR signaling results in the production of pro-inflammatory cytokines, such as Tumor Necrosis Factor (TNF) α and Interleukin (IL)-6, the activation of antigen presenting cells, and ultimately the induction of an adaptive immune response.

Peptides with a formylated methionine at their N-terminus, a signature of prokaryotic protein translation, bind with high affinity to FPRs (Dahlgren et al., 2016). Through this FPR interaction, bacterial N-formyl peptides act as chemoattractants, recruiting phagocytic cells, for example neutrophils, to the site of infection.

Inflammasomes are multiprotein complexes, typically composed of three components: a specialized sensor protein, the Apoptosis-associated Speck-like Protein containing a C-terminal caspase recruitment domain (ASC) adaptor molecule and caspase-1 (Ogura et al., 2006; Storek and Monack, 2015). Upon activation, caspase-1 induces an inflammatory response via the cleavage and secretion of the IL-1β and IL-18 cytokines, and by execution of a pro-inflammatory type of cell death